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CKJ REVIEW

An update review of intradialytic hypotension: concept, risk factors, clinical implications and management

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ABSTRACT

Intradialytic hypotension (IDH) is a frequent and serious complication of chronic haemodialysis, linked to adverse long-term outcomes including increased cardiovascular and all-cause mortality. IDH is the end result of the interaction between ultrafiltration rate (UFR), cardiac output and arteriolar tone. Thus excessive ultrafiltration may decrease the cardiac output, especially when compensatory mechanisms (heart rate, myocardial contractility, vascular tone and splanchnic flow shifts) fail to be optimally recruited. The repeated disruption of end-organ perfusion in IDH may lead to various adverse clinical outcomes affecting the heart, central nervous system, kidney and gastrointestinal system. Potential interventions to decrease the incidence or severity of IDH include optimization of the dialysis prescription (cool dialysate, UFR, sodium profiling and high-flux haemofiltration), interventions during the dialysis session (midodrine, mannitol, food intake, intradialytic exercise and intermittent pneumatic compression of the lower limbs) and interventions in the interdialysis period (lower interdialytic weight gain and blood pressure–lowering drugs). However, the evidence base for many of these interventions is thin and optimal prevention and management of IDH awaits further clinical investigation. Developing a consensus definition of IDH will facilitate clinical research. We review the most recent findings on risk factors, pathophysiology and management of IDH and, based on this, we call for a new consensus definition of IDH based on clinical outcomes and define a roadmap for IDH research.

Keywords: cardiovascular event, haemodialysis, intradialytic hypotension, roadmap, ultrafiltration

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INTRODUCTION

Despite recent advances in dialysis techniques, the high mortality of end-stage renal disease (ESRD) patients remains a major challenge, with most patients depending on haemodialysis (HD) to replace renal function [1]. Intradialytic hypotension (IDH) is one of the most common complications of HD in clinical practice due to the older average age of dialysis patients and the increasing prevalence of comorbidities such as diabetes mellitus and heart failure (HF). The prevalence of IDH ranges from 8 to 40% in different studies [2–5]. The reasons for the discrepant IDH prevalence in these studies are not completely known but might be due to using different definitions of IDH and/or to different patient characteristics [age, prevalence of diabetes or cardiovascular disease, interdialytic weight gain (IDWG), body weight and gender distribution]. While IDH causes huge patient distress during dialysis sessions, it is also strongly associated with vascular access failure, cardiovascular events, end-organ damage and mortality, emphasizing the need to optimize preventive and therapeutic strategies.

This review discusses the most recent findings on risk factors, pathophysiology and management of IDH. Based on this, we call for a new consensus definition of IDH, suggest a methodology for its development and propose a roadmap for IDH research.

IDH DEFINITION

Increasing our understanding of IDH is restricted by the absence of a consensus medical definition (Table 1). Definitions differ in the blood pressure (BP) parameter used [decrease in systolic BP (SBP), nadir SBP, decrease in mean arterial pressure (MAP)], the cut-off value for the BP parameter and the need for symptoms and/or intervention. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines in 2005 defined IDH as a decrease in either SBP ≥20 mmHg or MAP ≥10 mmHg leading to symptoms [6]. Other definitions given in different guidelines are (i) any episode of a decrease in BP during dialysis that requires an immediate intervention, like ultrafiltration reduction or saline infusion, (ii) a symptomatic decrease in either SBP ≥20 mmHg or MAP ≥10 mmHg that needs intervention and (iii) a symptomatic sudden drop in SBP ≥30 mmHg or a decrease in MAP ≥10 mmHg [14] . Similarly, the European Best Practice Guidelines (EBPGs) defined IDH as a decrease in SBP ≥20 mmHg in combination with clinical events and interventions [10]. An ideal definition should incorporate the concept of 'consequences for health', as does the chronic kidney disease (CKD) definition [15]. It may be argued that the development of symptoms and/or the need for intervention is already a consequence for health that may negatively impact quality of life. However, many databases do not accurately collect symptoms and nursing interventions that may additionally have a subjective component. Thus many studies prefer using a decrease in systolic BP by a specific amount (20, 30 and 40 mmHg) or nadir systolic BP below a threshold (90, 95 and 100 mmHg) [16]. When using only specific BP cut-off values, defining 'consequences for health' is even more necessary. In a recent study, Flythe *et al.* [16] evaluated the differences between various IDH definitions in the Hemodialysis (HEMO) and Large Dialysis Organization (LDO) study cohorts. In patients with pre-dialysis SBP <160 mmHg, nadir SBP <90 mmHg had the strongest association with mortality, while this value changed to nadir SBP <100 mmHg in patients with pre-dialysis SBP ≥160 mmHg. IDH definitions that contained symptoms, interventions or decreases in BP during the dialysis session were not associated with mortality [16]. However, caution should be exercised to possible confounders in observational studies, and randomized controlled trials are needed before a definitive definition of IDH can be established. Due to the lack of such evidence and consensus, the discrepancies in IDH definitions have hindered data collection for accurate estimation of IDH prevalence, risk factors and consequences, as well as for evidence-based strategies for IDH prophylaxis and treatment and the impact of such strategies on adverse clinical outcomes (Table 2).

PATHOPHYSIOLOGY OF IDH

IDH is the end result of the interaction between ultrafiltration rate (UFR), cardiac output and arteriolar tone. Thus excessive ultrafiltration may decrease cardiac output, especially when compensatory mechanisms (heart rate, myocardial contractility, vascular tone and splanchnic flow shifts) fail to be optimally recruited.

Ultrafiltration and total volume removal

Fluid extraction by ultrafiltration results in a sudden fluid compartment change that causes BP instability. The UFR is a key predisposing factor to IDH, especially when it exceeds the plasma refill rate, with the risk for IDH increasing greatly with

Table 1. Different definitions of intradialysis hypotension used in recent years

Definitions for intradialytic hypotension	Year	Decrease in SBP (mmHg)	Nadir in SBP (mmHg)	Decrease in MAP (mmHg)	Need for symptoms or intervention	Large epidemiological ($n > 1000$) or interventional ($n > 100$) study using this definition
KDOQI Clinical Practice Guidelines [6]	2005	≥20	ND	≥10	Symptoms	Retrospective cohort of 39 497 HD patients [7]
UK Renal Association Guidelines [8]	2011	Any	ND	Any	Immediate intervention	Cross-sectional study with 2193 HD patients [9]
European Best Practice Guidelines [10]	2007	≥20	ND	≥10	Symptoms and intervention	–
Japanese Society of Dialysis Therapy Guidelines [11]	2012	≥30	ND	≥10	Symptoms	–
Chou *et al.* [12], USA	2018	ND	<90	ND	ND	5-year cohort of 112 013 HD patients
Sands *et al.* [13], USA	2014	≥30 to a level of <90 mmHg	<90	ND	ND	Epidemiologic study of 1137 HD patients

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Table 2. EBPGs on haemodynamic instability 2007 [8]: key messages

Prevention of IDH
1. Evaluate patients for hydration status (prior to the session), frequently for BP and heart frequency rate (during the session) and, if frequent IDH episodes, for cardiovascular disease
2. Lifestyle interventions:
a. Decrease salt intake
b. Avoid food intake during or just before dialysis if frequent episodes of IDH, except if patient is malnourished
3. Dialysis technique
a. Optimize ultrafiltration
b. Avoid routine sodium profiling with supraphysiological dialysate sodium concentrations
c. Bicarbonate dialysis should be used
d. The use of a dialysate calcium concentration of 1.50 mmol/L should be considered and low-magnesium (0.25 mmol/L) dialysate should be avoided, especially in combination with low-calcium dialysate in patients with frequent episodes of IDH
e. Cool dialysate temperature dialysis (35–36°C) or isothermic treatments by blood temperature-controlled feedback should be prescribed in patients with frequent episodes of IDH
f. Haemo(dia)filtration techniques should not be considered a first-line option for the prevention of IDH, but as a possible alternative to cool dialysis
g. A prolongation in dialysis time or an increase in dialysis frequency should be considered in patients with frequent episodes of IDH
4. In patients with frequent episodes of IDH, antihypertensive agents should be given with caution prior to dialysis depending on pharmacodynamics, but should not be routinely withheld on the day of HD treatment
5. If other treatment options have failed, then consider switching to PD or midodrine or L-carnitine supplementation
Treatment of IDH
1. Trendelenburg position should be considered
2. Ultrafiltration should be stopped during an episode of IDH
3. Isotonic saline should be infused in patients unresponsive to stopping ultrafiltration and Trendelenburg position during an episode of IDH
4. Infusion of colloid solutions should be considered in patients who remain unresponsive to saline infusion

increasing gaps between UFR and plasma refill [17]. Higher UFR (>10–>13 mL/h/kg in different studies) were consistently associated with a higher incidence of IDH and mortality [18–20]. The rapid loss of volume overwhelms the compensatory mechanisms and the plasma refilling and venous return lag behind. Autonomic dysfunction or decreased contractility disrupt the compensatory mechanisms even further, thus patients with chronic heart failure (CHF) tend to develop IDH with lower UFRs [20]. Therefore, reducing the UFR either by increasing the time or frequency of dialysis sessions tends to decrease the occurrence of IDH [21]. On top of the UFR, rapid clearance of waste products during HD may lead to the formation of transient osmotic gradients, causing water loss from the extracellular to the intracellular space.

Decreased cardiac output

Decreased cardiac output has a key role in the pathophysiology of IDH. During HD, cardiac output depends on preload, afterload, heart rate and contractility. Changes in preload and afterload, determined mainly by intravascular volume and arteriolar vascular resistance, respectively, seem to play a major role in the development of IDH, while heart rate and contractility have a minor compensatory role [21]. However, the loss of compensation from increased contractility predisposes to the development of IDH in patients with CHF. Given that approximately one-third of HD patients have CHF at the time of initiation of dialysis therapy, a decrease in contractility is a prevalent risk factor for the development of IDH [22]. In a small study of 10 patients with no history of CHF or ischaemic heart disease, patients prone to IDH were found to have impaired myocardial contractility reserve assessed by response to dobutamine atropine stress [23]. While decreased myocardial function predisposes to the development of IDH, it is also shown that IDH itself causes myocardial stunning, a phenomenon known as reversible myocardial contractility due to ischaemia [23].

Arteriolar tone

A failure to maintain arteriolar tone during HD has been proposed to be a cause of IDH for >2 decades [24–26]. In normal physiology, a reduction in intravascular volume would lead to increased sympathetic outflow, thus to arteriolar vasoconstriction and increased peripheral vascular resistance, helping to maintain BP. Sympathetic discharge and baroreceptor sensitivity were hypothesized to be diminished in some HD patients [25, 27, 28]. In several studies, heart rate variability (HRV), a non-invasive method to estimate autonomic dysfunction, was used to assess sympathetic activity during HD. While HRV is increased during HD, signifying sympathetic activation, such a sympathetic response, was not seen in patients prone to IDH [29, 30]. Blunted sympathetic activation may hinder compensatory mechanisms and increase IDH incidence and severity. The prevalence of cardiovascular autonomic dysfunction in chronic HD patients was suggested to be as high as 50% [31].

In healthy individuals, plasma osmolarity is tightly regulated by thirst and arginine vasopressin (AVP) [32]. Since ESRD patients on HD have little to no renal response to AVP, baseline AVP levels in dialysis patients are higher than in healthy controls; however, they fail to increase in response to HD [33, 34]. The loss of the vasoconstrictive effect of AVP via activation of V1 receptors in vascular smooth muscle cells in HD patients may contribute to IDH, and this offers the opportunity for therapeutic intervention, as discussed below [35–37].

Suboptimal splanchnic blood flow shifts may also contribute to IDH. Monitoring of splanchnic blood shifts during HD using radiolabelled erythrocytes disclosed that within 30 min of ultrafiltration, a rapid central shift of the splanchnic blood pool was observed, possibly contributing to maintain BP values in the early phase of HD. A loss of such a shift in patients with autonomic dysfunction [38], as well as food ingestion, which causes a similar splanchnic sequestration [39], were suggested to predispose to IDH.

In the past, acetate was used as a dialysis solution base. Acetate has well-known vasodilator properties and therefore was an important cause of IDH historically [21]. Today, the use of bicarbonate-based dialysates has eliminated such predisposition around the world.

RISK FACTORS

Risk factors for the development of IDH include diabetes mellitus; cardiovascular disease including systolic and diastolic dysfunction, ischaemic heart disease, arrhythmias and vascular calcification; autonomic dysfunction; poor nutritional status;

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hypoalbuminaemia; female sex; age >65 years; pre-dialysis SBP <100 mmHg; high body mass index and severe anaemia [3, 28, 40].

High IDWG may also be a predisposing factor as it may require higher UFR [7]. In a retrospective study of 255 patients, absolute IDGW, but not percent IDGW, was a risk factor for IDH [41], while in a retrospective study of 39 497 patients, both absolute and relative IDGW were significant risk factors [7]. It was also suggested that the first HD session of the week was associated with a higher IDH risk in thrice-weekly HD [4]. In a cohort study of 293 patients with a 40% incidence of IDH, UFR, N-terminal pro-B type natriuretic peptide and β2 microglobulin were also found to be independently associated with IDH [2]. An ongoing cohort study that was expected to be completed by July 2019 recruited 90 participants to examine the correlation between diabetes status and IDH (ClinicalTrials.gov identifier NCT03870594). Further prevalence and risk factor studies are needed once a consensus definition of IDH is available that eliminates the current inconsistencies in the IDH definitions.

CONSEQUENCES OF IDH

IDH is associated with several significant clinical outcomes. The best established association of IDH is with cardiovascular events and mortality. In a retrospective study of 39 497 HD patient records, IDH was associated with myocardial infarction, hospitalization for HF/volume overload and cardiovascular and all-cause mortality [7]. Indeed, several studies have confirmed that IDH is an independent risk factor for all-cause mortality [2, 7, 12, 16, 42]. For instance, in a US-based cohort of 112 013 incident HD patients, a direct linear relationship between IDH and mortality was demonstrated, with a mortality hazards ratio (HR) of 1.49 [95% confidence interval (CI) 1.42–1.57] among patients who had IDH in >40% of their HD sessions [12]. However, there have also been reports to the contrary [43]. Such disagreeing results may be due to the different definitions of IDH used in many of those studies, including nadir intradialytic SBP <90 mmHg [12] and an SBP <90 mmHg associated with symptoms of hypotension and necessitating fluid administration [43].

IDH is independently associated with myocardial stunning, which in turn is associated with cardiovascular events and mortality [23, 44]. The reversible myocardial stunning due to repetitive reversible ischaemia within each IDH episode may initiate a pathway from myocardial hibernation to eventual irreversible myocardial fibrosis and irreversible systolic dysfunction [45]. The development of HF in HD patients predicts a significantly poorer outcome, and cardiovascular mortality is 30-fold more frequent in HD patients than in age-matched controls [46]. The management of IDH in patients with decreased left ventricular function can be challenging, as the acute management of IDH primarily consists of stopping ultrafiltration and administration of fluids [28], which may exacerbate an underlying HF. In such patients who are prone to myocardial stunning or already have myocardial dysfunction, IDH prevention is essential. Indeed, a randomized crossover study with 10 patients showed that dialysis-induced left ventricular regional wall motion abnormalities were improved by cooling the dialysate [46], a simple and effective method to decrease IDH incidence that is discussed below. Another randomized crossover study reported a similar significant decrease in left ventricular regional wall motion abnormalities along with significantly fewer IDH episodes in biofeedback dialysis, which modulated UFRs and dialysate sodium concentration in response to relative blood volume [47].

Another concern for HD patients with cardiac comorbidities is the dialysate calcium concentration. A recent retrospective cohort study observed that lower facility levels of dialysate calcium (<2.5 mEq/L) were associated with more frequent hospitalizations for HF exacerbation and also with more frequent IDH episodes [48]. Indeed, in prior reports, higher dialysate calcium concentrations were associated with an increase in left ventricular contractility in patients with normal cardiac function [49], as well as in patients with HF (New York Heart Association classifications III and IV) [50]. Intradialytic systolic and diastolic BPs were higher in patients receiving the dialysate with a higher calcium concentration (1.75 versus 1.25 mmol/L) [50]. However, the long-term effects of various IDH management strategies are subject to longitudinal clinical trials.

Another manifestation of end-organ damage caused by IDH is cerebral ischaemia. When BP and cerebral oxygenation were recorded during 635 HD sessions in 58 patients, every 10 mmHg decrease from baseline MAP was associated with a 3% increase in ischaemic events ($P < 0.001$), although no clear 'safe' MAP threshold could be determined, due to the presence of different cerebral autoregulation limits for each patient [51]. The potential clinical consequence of such repeated cerebral ischaemia was explored by Mizumasa *et al.* [52]. They assessed frontal atrophy indexes with magnetic resonance imaging in 32 HD patients twice after a 3-year interval and counted all IDH episodes during the same interval. The change in frontal atrophy indexes inversely correlated with the number of IDH episodes ($r = 0.45$, $P < 0.05$) [52]. In a 1-year long randomized clinical trial, patients treated with cooler dialysate (0.5°C below core body temperature) had fewer IDH episodes than patients on 37°C dialysate and showed no brain white matter changes after 1 year, while patients on 37°C dialysate exhibited the pattern of ischaemic brain injury (increased fractional anisotropy and reduced radial diffusivity) seen in HD patients [53]. Moreover, new evidence suggests that IDH-induced damage may cause dementia in the long term in older populations. In a cohort of 31 055 elderly HD patients, the cumulative exposure to frequent IDH was significantly associated with a 5-year risk of new-onset dementia. Patients who experienced seven or more episodes of IDH in 90 days had the highest 5-year risk of new-onset dementia [HR 1.36 (95% CI 1.20–1.48)] [54]. This possible association between cerebral ischaemia and IDH may explain the observation that cognitive impairment is more frequent in chronic HD than in peritoneal dialysis (PD) patients [55].

Mesenteric ischaemia and even liver ischaemia are rare forms of end-organ damage associated with IDH [56]. A case–control study including 626 patient with a hospitalized mesenteric ischaemia event and 2428 controls observed a direct association of the proportion of IDH (defined as nadir intradialytic SBP <90 mmHg) with hospitalized mesenteric ischaemia (P for trend = 0.001) [57]. Several previous case series studies of HD patients also described hypotensive episodes preceding mesenteric ischaemia events [58, 59]. Similarly, case reports have observed other rare complications of chronic HD occurring immediately after IDH episodes. For example, a patient develops non-arteritic anterior ischaemic optic neuropathy three times in 4 months; each episode was noticed at the end of a dialysis session complicated by IDH [60].

IDH accelerates the loss of residual renal function (RRF). RRF preservation has strong survival benefits in both PD patients [61] and HD patients [62]. RRF has a significant role in fluid balance, toxin clearance and calcium–phosphorus metabolism and its decline is associated with more severe anaemia, inflammation and malnutrition as well as cardiovascular morbidity and

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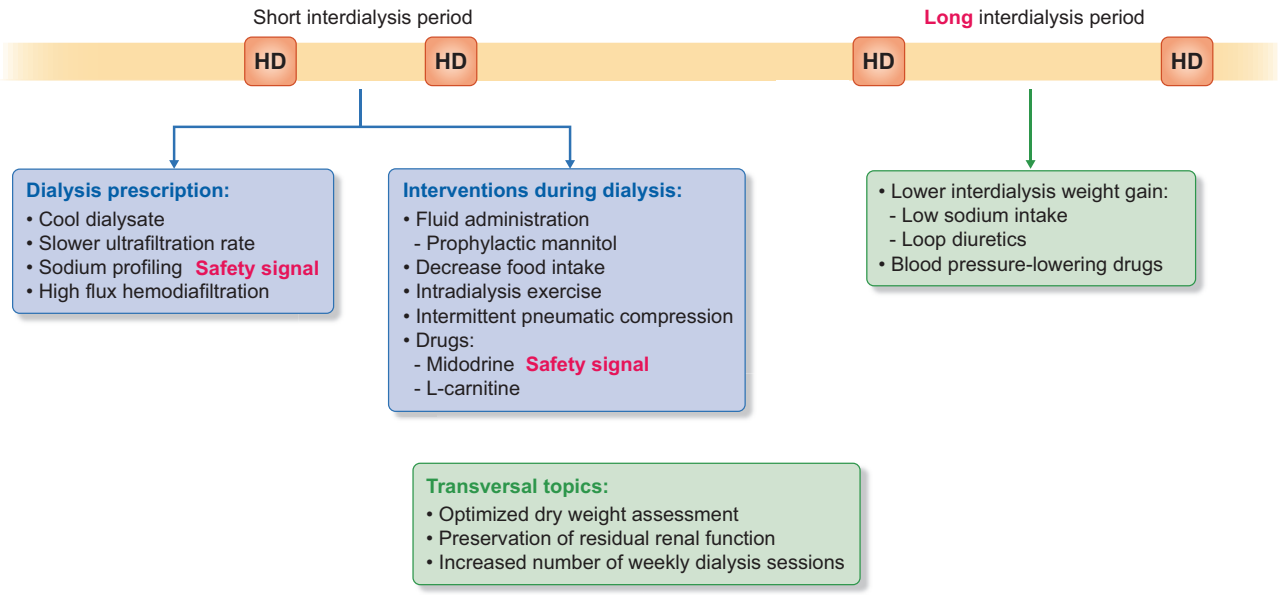

FIGURE 1: Approaches to prevent and treat intradialysis hypotension. Approaches in which a safety signal has been described suggesting that outcomes may be impaired are indicated by the red 'Safety signal'.

mortality [17]. Because RRF is lost more rapidly in patients on HD than in patients on PD [61], IDH is a suspected driver of this crucial difference. In a prospective study with 279 incident dialysis patients, IDH was independently associated with a faster renal function decline rate in the first 3 months of HD [63]. Given that the decline in RRF is greater during the first 3 months [64], IDH should be avoided in new dialysis patients with higher RRF. As these patients have residual diuresis, a key factor is to avoid excessive ultrafiltration.

IDH was also associated with vascular access thrombosis, a very troublesome complication for chronic HD patients [65]. In the HEMO study cohort of 1426 HD patients, the highest quartile of IDH had an ~2-fold higher independent relative rate of native arteriovenous fistula thrombosis than the lowest quartile during a median of 3.1 years. However, IDH was not associated with prosthetic arteriovenous graft thrombosis [65].

Besides the detrimental long-term consequences, IDH is a major cause of distress in patients during the HD sessions, as it may cause lightheadedness, weakness, headache, nausea and vomiting [66]. Although definitions of IDH based solely on the magnitude of decrease in SBP do not sufficiently capture patient symptoms, these are a major determinant of quality of life in dialysis patients [67]. In addition, such symptoms may cause the HD session to be terminated earlier, resulting in inadequate toxin and fluid elimination.

PREVENTION AND TREATMENT

Several approaches have been suggested to decrease the incidence or severity of IDH. These include optimization of the dialysis prescription (cool dialysate, UFR, sodium profiling, high-flux haemofiltration), interventions during the dialysis session (midodrine, fluid administration, food intake, intradialytic exercise and intermittent pneumatic compression of the lower limbs), interventions in the interdialysis period (lower IDWG and BP-lowering drugs) and switching the modality to PD (Figure 1).

Cool dialysate

Reducing the temperature of the dialysate below the core body temperature is one of the most-used preventive methods against IDH. In fact, EBPGs recommend the use of cool dialysate as a first-line option to prevent IDH [10] (Table 2) . Cool dialysate decreases the risk of IDH development by inducing vasoconstriction and activating the sympathetic nervous system [68]. In a meta-analysis of 26 trials including a total of 484 patients, cool dialysis reduced the rate of IDH by 70% (95% CI 49–89) and increased intradialytic BP by 12 mmHg (95% CI 8–16), while the adequacy of dialysis was not affected, with no significant difference in K_t/V_{urea} [69]. Similarly, a systematic review of 22 studies including 408 patients determined that IDH occurred 7.1-fold (95% CI 5.3–8.9) less frequently and post-dialysis MAP was 11.3 mmHg (95% CI 7.7–15.0) higher with cool dialysis. Moreover, none of the studies showed a reduction in urea clearance, a measure of dialysis adequacy, with cool dialysate [70]. In clinical trials, cool dialysate was also reported to prevent IDH-related complications such as myocardial stunning [46], HD-associated cardiomyopathy [71] and HD-related brain white matter changes [53]. While the efficacy of cool dialysate is proven in chronic HD patients, its efficacy in preventing IDH in acute kidney injury (AKI) patients receiving sustained low-efficiency dialysis will be assessed in an ongoing randomized trial with 38 patients (ClinicalTrials.gov identifier NCT03397992), following previous promising results [72]. Using cool dialysate is completely safe, simple and entails no additional costs. The one drawback is the unpleasant sensations described by many patients, which reduce patient tolerability [69]. Nevertheless, an anecdotal small study of 10 HD patients reported that 8/10 patients who experienced cool dialysate (35°C) for three sessions felt more energetic after those dialysis sessions and

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requested to be always dialysed with cool dialysate [73]. Assessment of patient expectations and patient education before the introduction of cool dialysate may be beneficial for increasing patient tolerance. Alternatively, individualizing cool dialysate temperature to individual pre-dialysis core body temperatures still maintained the beneficial effects on intradialysis BP and myocardial stunning, while causing no patient distress [74].

UFR

Recent studies have consistently shown the detrimental effects of higher UFR on the incidence of IDH and cardiovascular/all-cause mortality [19, 20, 75]. Thus, decreasing UFR is a promising intervention. The Dialysis Outcomes and Practice Patterns Study (DOPPS), which included 22 000 HD patients from seven countries, found that a UFR >10 mL/h/kg correlated with higher odds of IDH [odds ratio (OR) 1.30; P = 0.045] and a higher risk of all-cause mortality (relative risk 1.09; P = 0.02), while there was no association between UFR and cardiovascular mortality [18]. A smaller study of 287 HD patients also found that high UFR was independently associated with mortality (HR 1.22, P < 0.0001) and estimated a relative receiver operating characteristic curve cut-off value of 12.4 mL/h/kg UFR for predicting death within 5 years [19]. Flythe *et al.* [20] compared three categories of UFR for associated mortalities: UFR <10, 10–13 and >13 mL/h/kg. The risk of all-cause and cardiovascular mortalities began to increase at UFRs >10 mL/h/kg in spline analysis. Of note, all studies so far were observational. Thus they did not completely exclude the existence of potential confounders, such as RRF, that explain the association between UFR and mortality [75]. In this regard, the issue will only be settled by randomized controlled clinical trials that explore whether decreasing IDH by decreasing UFR has an impact on mortality.

Nevertheless, in 2015 the Kidney Care Quality Alliance set two fluid-related quality measures, including avoidance of high UFRs (≥13 mL/h/kg), hoping to decrease the incidence of IDH, end organ damage in the heart, brain and kidney and mortality [19, 20, 75]. Decreasing the UFR may be achieved by having longer or more frequent dialysis sessions, which may deter many clinics and patients from such an intervention, or by limiting interdialysis weight gain (discussed below) [75]. The introduction of biofeedback mechanisms may limit the impact on dialysis session duration or frequency by individualizing the UFR continuously in response to momentary BP and blood volume changes. Most biofeedback devices continuously monitor BP or estimate plasma refilling from the relative blood volume calculated from haematocrit changes. This information is then processed by the software to adjust the UFR and conductivity accordingly. In a meta-analysis including eight studies, biofeedback significantly decreased the incidence of IDH [risk ratio 0.61 (95% CI 0.44–0.86)] [76]. However, the evidence for an effect on mortality lacked sufficient power for evaluation [76]. Large randomized clinical trials are required to assess the impact of biofeedback devices on hard outcomes.

Accurate estimation of target dry weight is crucial for every HD patient. Although it is usually done clinically, novel methods assess target dry weight objectively, including bioelectrical impedance spectroscopy (BIS), lung ultrasonography (US) and measurement of the inferior vena cava [77–80]. BIS measures the fluid status through the body resistance to electrical currents. In a cross-sectional study including 194 HD patients, patients who had hypovolaemia by multifrequency bioimpedance developed more frequent IDH episodes [81]. BIS can be used to identify patients prone to IDH and prevent IDH development, as well as to routinely assess post-dialysis target dry weight. In a randomized controlled trial including 298 Asian HD patients, BIS-based post-dialysis target weight assessment significantly lowered the incidence of IDH when compared with clinical-based assessment (6.10 versus 6.62%, P < 0.05) and improved hypertension control, while the incidence rate for all-cause hospitalization and mortality did not significantly differ [82]. Another randomized control trial of 131 HD patients observed a greater decline in relative fluid overload and carotid and femoral pulse wave velocities, a marker of arterial stiffness, in the bioimpedance-assessed group than in the clinically assessed group after 2.5 years, which indicated improved cardiovascular end points, while the frequency of IDH between the groups did not differ [83]. In 2017, a meta-analysis on the effect of bioimpedance-estimated dry weight on mortality in HD patients revealed no association between the use of BIS and all-cause mortality [84].

Besides BIS, lung US is emerging as a reliable and non-invasive estimate of body fluid status. Lung US detects lung congestion using the B-line score, a straightforward yet training-requiring tool [85]. While the use of BIS and lung US are accepted as accurate tools to assess volume overload [85, 86], their long-term outcomes and associations with IDH are yet to be confirmed. In a randomized clinical trial including 250 HD patients, dry weight assessment based on lung US with bioimpedance was not superior to clinical assessment in terms of all-cause mortality, cardiovascular outcomes or IDH frequency [79].

Sodium profiling

The ideal sodium concentration of dialysate has long been a topic of discussion [87]. Waste removal by diffusion during HD decreases extracellular fluid osmolarity and causes a shift of extracellular fluid into cells. Such a shift is avoided by raising dialysate sodium concentrations, which restores the osmotic gradient and plasma refill. Yet, increasing the sodium concentration causes thirst and volume expansion and increases BP [88]. Excess sodium has additional adverse consequences, independent of its osmotic effects, such as increasing endothelial cell stiffness [89], impairing nitric oxide release [89] and increasing sympathetic outflow [90]. Sodium profiling is proposed to limit such negative effects. During sodium profiling (modelling), dialysate sodium concentration is high in the beginning of the dialysis session and is gradually decreased as waste solutes are cleared from plasma. In a meta-analysis of 10 studies comparing two methods of sodium modelling, stepwise profiling significantly reduced IDH, while linear sodium profiling did not [91]. A more recent randomized, triple-blind, crossover clinical trial randomly assigned 80 patients to four different combinations of sodium modelling (decreasing from 150 to 138 mmol/L) and/or a dialysate temperature reduction (35°C) in changing orders. The two treatment schedules that included sodium profiling reduced the number of IDH episodes when compared with control or cool dialysate, while cool dialysate reduced IDH episodes compared with standard dialysis but had no additive effect on sodium profiling [92]. Yet, interdialysis weight gain was not reported, possibly obscuring the negative effects of sodium profiling. Thus, despite the positive impact of sodium profiling on IDH episodes, a recent analysis of the DOPPS cohort, which included 10 250 patients in 273 international facilities, showed that the routine use of sodium profiling to prevent IDH was actually associated with higher all-cause and cardiovascular mortality [HR 1.36 (95% CI 1.14–1.63) and HR 1.34 (95% CI 1.04–1.73),

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respectively] [93]. Due to the conflicting evidence and concerns about safety, EBPGs currently do not recommend sodium profiling [10] (Table 2).

High-flux haemofiltration

High-flux convection was suggested to reduce IDH episodes when compared with diffusive techniques like low-flux HD [94]. In two consecutive studies by the Sardinian Collaborative Group, pre-dilution online haemofiltration was associated with fewer IDH episodes than high-flux HD ($P < 0.04$ and $P = 0.003$, respectively) [95, 96]. A more recent mult-centre, open-label randomized study assessed the number of IDH episodes in 146 long-term dialysis patients on low-flow HD, online pre-dilution haemofiltration and/or haemodiafiltration. The frequency of IDH episodes increased for HD (from 7.1 to 7.9%) and decreased for haemofiltration (from 9.8 to 8.0%) and, above all, for haemodiafiltration (from 10.6 to 5.2%) ($P < 0.001$) when compared with the run-in HD period. However, the pre-dialysis SBP significantly increased in the haemodiafiltration group, suggesting a positive sodium balance as an explanation for the decreased IDH episodes [94]. The impact of haemodiafiltration on mortality is still controversial, despite a clinical trial concluding that high-efficiency post-dilution online haemodiafiltration reduces all-cause mortality in HD patients [97–99].

Midodrine

Midodrine is an oral prodrug alpha 1 adrenergic receptor agonist that is removed via HD with a half-life of 3 h [100]. In a meta-analysis including 117 patients from 10 studies, midodrine was associated with a 13.3 mmHg (95% CI 8.6–18.0) higher nadir SBP, and 6/10 studies reported improved IDH symptoms. No adverse effects were reported, but the number of patients studied was too low [101]. In this regard, in a recent retrospective observational study of 1046 patients who were prescribed midodrine for IDH and 2037 controls it was found that midodrine use was associated with a higher adjusted incidence rate ratio of mortality [1.37 (95% CI 1.15–1.62)] and all-cause and cardiovascular hospitalization [1.31 (95% CI 1.19–1.43) and 1.41 (95% CI 1.17–1.71), respectively]. Although the models were adjusted for the presence of cardiovascular morbidities and residual confounding may affect the results [102], the safety signal identified suggests that midodrine should not be routinely used for IHD until prospective clinical trials confirm its safety and efficacy.

L-carnitine

L-carnitine transports cytosolic long-chain fatty acids as acylcarnitines across the inner mitochondrial membrane for β-oxidation and subsequent adenosine triphosphate production in the mitochondria and thus it is required for optimal energy production by, among others, cardiovascular cells. As with other molecules, it may be lost in the dialysate and it was suggested that L-carnitine supplementation may prevent IDH and European best Practice quidelines (EBPGs) state that 'carnitine supplementation should be considered for the prevention of IDH if other treatment options have failed' [10]. However, a 2008 meta-analysis of five studies concluded that the available evidence does not confirm a beneficial effect of L-carnitine supplementation on IDH [103] and a more recent randomized clinical trial enrolling 92 patients that had IDH as a secondary endpoint did not find any differences between intravenous L-carnitine and placebo [104]. However, an even more recent, but small trial ($n = 33$, $n = 7$–10 per group) enriched in patients with a past history of IHD did observe significantly fewer IDH episodes in patients supplemented with intravenous L-carnitine prior to the HD session [105]. We should be aware that oral L-carnitine supplementation may result in the increased formation of the uraemic toxin trimethylamine N-oxide [106].

Fluid administration

Fluid administration, including colloids and crystaloids, has long been used to reverse IDH. Isotonic saline administration is problematic since it limits the achievement of a negative fluid balance. Hypertonic saline and colloids, including albumin, have also been used during the episode [107]. Mannitol is a well-known medication to boost intravascular volume [100], although its efficacy as a therapy and prophylactic agent for IDH is questionable [108]. In a prospective study including 102 patients, routine (preventive) mannitol administration before the dialysis session was associated with a 5.4 mmHg higher nadir SBP ($P = 0.03$), 25% less decline in SBP ($P = 0.03$) and 50% lower odds of having a hypotensive event [OR 0.50 (95% CI 0.29–0.83)] in adjusted models [109]. However, a double-blind randomized controlled trial by the same group enrolling 52 patients could not confirm the effect of mannitol administration on SBP decline during dialysis sessions and the decrease in IDH risk was of borderline significance ($P = 0.05$) [110]. Of note, neither study addressed the impact on volume overload or long-term effects.

Food intake

The overall impact of food consumption during the HD session on IDH is controversial. Given that malnutrition and hypoalbuminaemia are prevalent in ESRD patients undergoing dialysis, commonly referred to as protein-energy wasting, and are strong predictors of mortality, in-centre supplementation of high-protein meals during HD appears to be practical and cost effective [111]. Yet there are concerns about an increased incidence of IDH with such intervention. In an observational study including 166 HD patients, food and fluid consumption during dialysis sessions was a strong predictor for IDH ($P = 0.003$) and the need for mannitol use ($P = 0.000$). The consumption of >200 calories increased the risk of IDH 2-fold, but this was not statistically significant ($P = 0.058$) [112]. Similarly, a randomized crossover study of 13 patients reported an increased incidence of symptomatic IDH requiring intervention with food intake during dialysis ($P = 0.025$) [113]. These results can be explained with the hypothesis that increased splanchnic blood flow predisposes to IDH due to redistribution of blood volume, as discussed above. However, another observational study including 126 HD patients found no correlation between food intake and the number of IDH episodes [114]. Additionally, in a very recent non-randomized parallel-arm study including 18 HD patients, a high-protein meal during dialysis sessions did not change the frequency of symptomatic IDH. The different results may depend on the population studied (general dialysis populations versus IDH-prone individuals), the local HD session prescription practices and the nature of the food provided. Larger, long-term studies are warranted that explore the impact of high-protein supplementation during dialysis in individuals prone to IDH.

Intradialytic exercise and intermittent pneumatic compression of the lower limbs

Intradialytic exercise has been studied recently as a new promising therapy for IDH. In a randomized trial including 22 HD patients, a combination of aerobic exercise with bicycle

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ergometer and anaerobic exercise with elastic bands decreased the incidence of IDH ($P < 0.05$) [115]. A randomized crossover study of 21 HD patients compared the effects of cyclic exercise and intermittent pneumatic compression of the lower limbs during the first hour of dialysis sessions with controls (no intervention). Only pneumatic compression significantly decreased IDH frequency (24% versus 43% of control patients, $P = 0.014$), while the modest reduction with exercise (38% of patients) was not statistically significant [116]. A recently completed (30 April 2019) randomized crossover clinical trial including 112 HD patients evaluated the impact of early versus late (during the HD session) intradialytic exercise on IDH, but results are not currently available (ClinicalTrials.gov identifier NCT03504943). Further investigations on the utility of pneumatic compression for IDH are warranted.

Lower IDWG

Since the rapid loss of volume by ultrafiltration is one of the main drivers of IDH, restricting the IDWG is one approach to prevent IDH. Preservation of RRF by avoiding the use of nephrotoxic agents and excessive ultrafiltration in incident dialysis patients is the key to maintain low IDWG for longer periods. Dietary sodium restriction is also a key factor limiting IDWG. This is a key concept that should be carefully explained to incident patients and new dialysis unit staff: there is a widespread misconception that the key to low IDWG is low fluid intake; however, thirst will make impossible any attempt at decreasing fluid intake when there is no concomitant dietary sodium restriction. Furthermore, education on occult sources of sodium is necessary, as well as dietary recommendations for alternative flavouring agents. Unfortunately, sodium restriction is not always possible to accomplish in daily practice. Low-salt processed foods are hard to find, patients may not be able to cook with raw ingredients and their long-established dietary preferences frequently prevent such personal sacrifice [117]. Nevertheless, strict salt restriction resulted in less frequent IDH episodes, lower left ventricular mass and less left ventricular hypertrophy compared with antihypertensive drug usage [118]. In patients with RRF, high-dose furosemide, as practiced in some countries, may increase urine output and decrease IDWG [119].

BP-lowering drugs

As many as 50–90% of ESRD patients suffer from hypertension [120] and finding the balance between antihypertensive management and IDH risk can be a huge challenge. The mainstream practice is withholding BP-lowering medications prior to HD sessions [120]. In a UK-based cohort study of 2630 HD patients, the number of IDH episodes was significantly higher in patients who were not on antihypertensive drugs than in patients on antihypertensive drugs [121]. The pre-dialysis BP values in the two groups were not significantly different, but it is not possible to eliminate the bias arising from the different haemodynamic characteristics of the patients who do and do not need antihypertensive medications to achieve the same BP target. A small double-blind crossover study with 10 patients assessed the effect of verapamil, a non-dihydropyridine calcium channel blocker, administered 1 h before dialysis on the occurrence of IDH. Verapamil was chosen because of its benefits on left ventricular compliance and relaxation, with less pronounced vasodilatory effects. Two 2-week verapamil periods alternated with two 2-week placebo periods. No significant difference was found in the severity or frequency of IDH episodes between the periods [122]. Another study monitored the initiation of atenolol in eight hypertensive HD patients. The drug was given thrice weekly at the end of each HD session and the study found MAP was successfully reduced with no effect on IDH [123]. However, the drug was administered at the end of HD sessions and not in between, thus not directly exploring the impact of same-day, prior-to-HD-session antihypertensive drugs and IDH. In a study with 21 hypertensive HD patients, the incidence of IDH episodes did not increase after the addition of antihypertensive medications [124]. A similar result was found in a randomized, placebo-controlled trial including 251 hypertensive HD patients, where the administration of amlodipine 10 mg did not cause a significant difference in the frequency of IDH episodes while successfully decreasing mean pre-dialysis BP [125]. Of note, these studies only included hypertensive patients who needed BP-lowering medications, presumably hypotension-resistant patients. Current evidence is not enough to assess the benefits and disadvantages of withholding antihypertensives and to compare IDH risks of different antihypertensive medications.

Switching to PD

The ultimate solution to intractable IDH is changing the dialysis modality to PD, since IDH is mainly a complication of HD and is not seen in PD. A careful assessment of the potential barriers for PD and the patient's desire to perform self-care is needed.

LIMITATIONS AND A ROADMAP FOR IDH RESEARCH

Currently the most important limitation of IDH research is the lack of a consensus IDH definition. Current definitions based on symptoms and/or interventions are clinically relevant but not well suited for large-scale studies. This is also the case for definitions in other fields of nephrology. For example, the AKI definition based on urinary output is not well suited for large-scale studies. Thus we propose to develop a novel consensus definition using large-scale data focused on both short-term (hospitalization) and long-term (mortality) outcomes. That is, as for other definitions, ranging from hypertension and hypercholesterolaemia to chronic kidney disease or AKI, the consensus definition should be based on the implications for health, i.e. on the risk for adverse outcomes, of specific BP thresholds. The definition may have two aspects: a threshold BP to define an individual IDH episode and a frequency parameter identifying what number of IDH episodes per unit of time is clinically relevant. Ideally, the threshold BP to define an individual IDH episode should be based on big data analysis and may be represented by an absolute drop in systolic or mean BP, by a percentage drop in systolic or mean BP over baseline, by an absolute SBP nadir or by a BP nadir that represents a percentage of baseline values, among others. Thus we should be open to novel concepts regarding the definition of a BP threshold. A consensus IDH definition usable in large databases may facilitate the development of larger, long-term prospective observational studies or clinical trials that would provide evidence-based indicators of IDH and guidelines for the prevention and treatment of IDH [14] (Figure 2).

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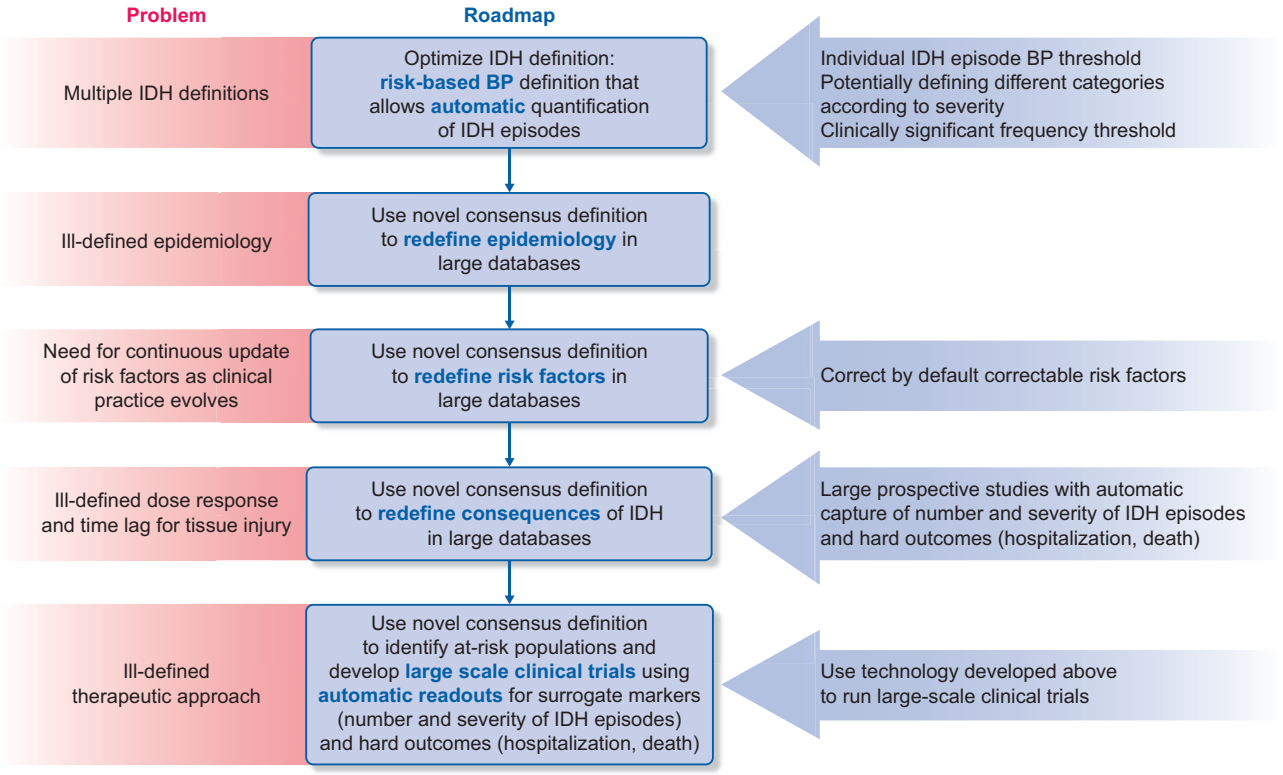
Problem
Roadmap
Multiple IDH definitions
Optimize IDH definition: risk-based BP definition that allows automatic quantification of IDH episodes
Individual IDH episode BP threshold
Potentially defining different categories according to severity
Clinically significant frequency threshold
Ill-defined epidemiology
Use novel consensus definition to redefine epidemiology in large databases
Need for continuous update of risk factors as clinical practice evolves
Use novel consensus definition to redefine risk factors in large databases
Correct by default correctable risk factors
Ill-defined dose response and time lag for tissue injury
Use novel consensus definition to redefine consequences of IDH in large databases
Large prospective studies with automatic capture of number and severity of IDH episodes and hard outcomes (hospitalization, death)
Ill-defined therapeutic approach
Use novel consensus definition to identify at-risk populations and develop large scale clinical trials using automatic readouts for surrogate markers (number and severity of IDH episodes) and hard outcomes (hospitalization, death)
Use technology developed above to run large-scale clinical trials

FIGURE 2: IDH roadmap 2020. Roadmap towards a risk-based consensus definition of IDH based of BP values that predict outcomes and allow large-scale analysis of risk factors, impact on outcomes, selection of high-risk populations for interventional studies and assessment of impact of interventions. Different BP-related variables should be explored as predictors of outcomes and thus as potential components of the IDH definition. These include threshold for SBP, BP nadir, percentage change below baseline BP and others, including MAP values. Thresholds to grade the severity of the episodes should also be defined in a similar manner as we have different categories of AKI or CKD according to severity. In addition, the number of such IDH episodes per time period that is clinically relevant for outcomes risk should also be defined.

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CONFLICT OF INTEREST STATEMENT

None declared.

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